Review

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Posted Date: 12 December 2023

doi: 10.20944/preprints202312.0820.v1

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Aberrant Hippocampal Neuroregenerative Plasticity in Schizophrenia: Reactive Neuroblostosis as a Possible Pathocellular Mechanism of Hallucination

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Abstract: Schizophrenia is a spectrum of neuropsychiatric deformities, characterized by hallucination, delusion, mood disorders, speech pathology, and neurocognitive deficits. Among various clinical manifestations, hallucination has been recognized as a core psychotic symptom that occurs more frequently in schizophrenia. A significant number of subjects with neurocognitive disorders like Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and other neurological diseases like stroke and epileptic seizure also experience hallucinations. While aberrant neurotransmission has been linked to the neuropathogenic events of schizophrenia, the specific cellular mechanism contributing to hallucinations remains ambiguous. Neurodegeneration in the hippocampus of the brain has been identified as a predominant pathogenic determinant of dementia. While the scientific proof for the neurodegeneration in schizophrenia is limited, the occurrence of dementia in schizophrenia has become increasingly evident. To note, both neurodegenerative, neurodevelopmental, and neuropsychiatric disorders display impaired neurogenesis in the brain. Impaired neurogenesis in the hippocampus has been linked to dementia and mood disorders. Notably, the early phase of many neurodegenerative disorders has been characterized by reactive neuroblostosis and aberrant cell cycle activation in mature neurons leading to the fluctuation in neurogenic processes leading to abnormal synaptogenesis and neurotransmission in the brain. Thus, this article emphasizes a hypothesis that aberrant neurogenic processes could be an underlying mechanism of hallucination in schizophrenia and other neurological diseases.

Keywords: schizophrenia; hallucination; neurogenesis; reactive neuroblastosis; dementia

Introduction

Schizophrenia is a debilitating neuropsychiatric disorder, characterized mainly by hallucination, delusions, mood disorders, and cognitive deficits[1–3]. Initially, Emil Kraepelin described the clinical features of this peculiar affective disorder as dementia praecox, and manic depression due to the admixer of behavioral deformities overlapping with various mental illnesses [4]. Later on, the term schizophrenia was suggested by Eugen Bleuler in 1908 and provided a further description of the different positive and negative psychotic symptoms [2,5]. While frequent episodes of hallucinations, delusions, paranoia, abnormal exhilaration, irrational thinking, and inexplicable behaviors are the positive symptoms of schizophrenia, the obvious negative symptoms comprise speech disorders, apathy, emotional blunting, catatonia, depression, and suicidal thoughts. Considerable degree of memory loss, deterioration of interpersonal skills, and attention deficits are the key cognitive deficits noticed in schizophrenia [1,2,4,6].

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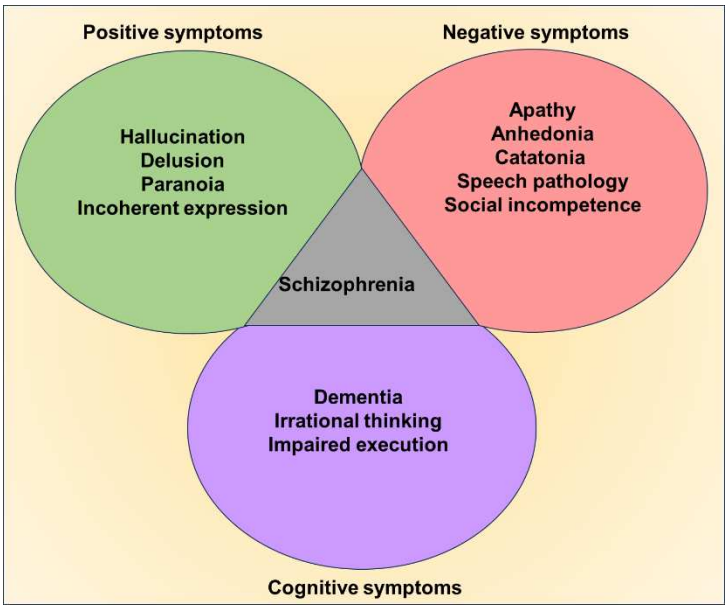

Figure 1. Clinical symptoms of schizophrenia; The digital highlights the key clinical manifestations of schizophrenia, the positive, negative, and cognitive symptoms.

While the schizoid symptoms in childhood are rare, subtle prodrome signs appear to develop in the late teenage and thus marked degree of altered behavioral patterns is distinguishable in a significant percentage of individuals during their fourth decade of life[6,7]. The prevalence of schizophrenia is almost 1% of the global population regardless of gender and ethnicity [1,8]. Presently, there are no structured diagnostic strategies and confirmative biomarkers available to delineate the behavioral symptoms and pathogenesis of schizophrenia, because the etiology of the disease is not distinctive, the psychotic patterns are comorbid, vary among patients, and differ over time. The symptoms of schizophrenia appear to often be co-occurred with psychosis, BPD, OCD and MDD [9,10]. Despite the accumulation of enormous clinical reports and case studies, the precise etiology and distinguished pathogenic mechanisms accountable for the onset and progression of schizophrenia remain to be established. Also, the screening strategies for prenatal diagnosis and preventive measures for schizophrenia are highly limited. Thus, the therapeutic targets for establishing an effective curative regime remain ambiguous. The available interventional medications such as tailored combinations of antipsychotics, antidepressants, and anxiolytic agents are aimed at merely handling behavioral disorders through modulation of aberrant neurotransmission in the brain [1,11]. Moreover, many neuropharmacological approaches implemented for schizophrenia pose unforeseen adverse effects rather than a cure [1,12]. Therefore, there is a crucial need for scientific advancement in deciphering the underlying pathogenic determinants of schizophrenia which would help in identifying the ultimate therapeutic target. Reactive astrogliosis, an overpopulation of pathogenic astrocytes has widely been regarded as a non-neuronal pathogenic consequence leading to disruption of brain homeostasis and creating an imbalance in neurotransmitters during clinical episodes of various mental innless [13]. Though experimental evidence highlights the alterations in the expression of astrocyte-related genes, the reports on the abnormal astrogliogenic events in schizophrenia are inconsistent [13–16]. Thus, the involvement of astrocytes in the pathogenic events in schizophrenia remains to further be established. Besides, a prominent histopathological signature for the activation of microglial cells, in part responsible for neuroinflammation has also increasingly been evident in the brains of schizophrenic subjects [17,18]. The progressive neuroinflammatory process has been known to impair the ongoing neurogenic process in the brain [19–21]. Ample experimental evidence suggests dysregulation of adult neurogenesis, is a prominent pathogenic characteristic of various neurodegenerative, mood, and psychiatric disorders that include Alzheimer's disease (AD), Huntington's disease (HD), Parkinson's disease (PD), stress, depression, anxiety, and schizophrenia [20,22–26]. While the

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progressive decline in hippocampal neurogenesis contributes to the pathomechanisms of dementia and mood disorders, ample experimental evidence demonstrated the occurrence of reactive neurogenesis in the early phases of many neurodegenerative and psychiatric disorders that include AD, PD, HD, and schizophrenia [27–31], Neuroblasts have been considered as immature neurons, derived from the neuronal stem cells of the developing as well as the adult brain [32,33]. The amount of neuroblasts produced in the brain determines the degree of terminal neurogenic process in the adult brain accounting for various neurogenerative plasticity and brain repair [32]. Recently, a new line of emerging scientific evidence underpins an abnormal activation profile of neural cells namely reactive neuroblostosis that depicts the overproduction of immature neurons leading to aberrant neurogenesis in the early phase of many neurodegenerative disorders that display movement disorders and dementia including AD and HD [27,33–36]. As these neurodegenerative disorders progress into the later stages, the neuroblastosis events appear to be diminished due to the depletion of neural precursor cells or degeneration of the neuroblasts [33–35,37]. Notably, traumatic brain injury, cerebral stroke, and epileptic seizure have also been characterized by reactive neuroblostosis and subsequent abnormal migration of mitotically active neuroblasts in the affected regions of the brain [36,38–40]. However, the role of reactive neuroblastosis in the pathogenic process or brain repair remains ambiguous. As the ultimate cell fate of reactive neuroblasts is uncertain, reports on their possible involvement in the disease progression, and cognitive, and psychiatric alterations are limited. To note, the fluctuation in the regulation of neurogenesis resulting from reactive neuroblasts in the adult brain could alter and deteriorate the neuroplasticity responsible for mental health and behavior including memory and mood.

Risk factors and etiopathological relevance of schizophrenia

The clinical manifestations of schizophrenia appear to originate from multifactorial elements including some definitive and mostly unknown gene mutations, copy number variations, epigenetic alterations, dysregulated transcriptomics, chromosomal abnormalities, metabolic defects, abnormal brain development, synaptic dysfunctions, aberrant neurotransmission, abnormal lifestyle, environmental factors [2,41]. Notably, maternal malnutrition, preeclampsia, gestational diabetes, prenatal viral infections, vitamin D deficiency, twin gestation, emergency cesarean section, childbirth complications, birth during the winter season, low birth weight, autoimmune diseases, chronic mood disorders, asphyxia, air pollution, illiteracy, and substance abuse, living in an urban area, immigration to the foreign country, living in unsuitable environment and transcultural influences have been identified as the key risk factors for schizophrenia [2,42–45]. Thus, the etiology and risk factors of schizophrenia are highly multifaceted. While the shreds of evidence for pathogenic signatures of neurodegeneration in schizophrenia-affected brains are indecisive, the neurodevelopmental hypothesis has been considered in which early neurogenic defects and aberrant migration of neuronal precursor cells have been emphasized as underlying psychotic symptoms and cognitive deficits at the later stage of life accounting for schizoaffective disorders [46]. Embryonic stem cells derived from early neurogenesis through the generation of neuroblast cells are an important aspect of brain development during embryogenesis [47]. The abnormal in-utero condition affecting brain development at the level of neuroblast formation and migration has been considered a prime risk factor for schizophrenia [48,49]. Eventually, several theories have been postulated for the neuropathogenic basis of schizophrenia. Disruption of glutamate transmission in the thalamocortical areas has been linked to the development of schizophrenia. Various experimental evidence gathered from the use of anesthetic agents namely phencyclidine and ketamine suggest that defects in the expression and function of glutamate decarboxylase (GAD)-1, hypofunction glutamate, and N-methyl-D-aspartate (NMDA) receptors are associated with the development of schizophrenia [50,51]. While glial cells are important for the neurotransmission of glutamate at the synapses, abnormal gliogenic events during brain development have also been proposed to be involved in the progression of schizophrenia [52]. Further, unusual flux in the release of dopamine and differential expression of its receptors in mesolimbic areas, nigrostriatal, and mesocortical tracts have also strongly been coupled to the symptomatic signature of schizophrenia [53]. As increased release and

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hyper-transmission of dopamine in the subcortical area of the brain is known to contribute to positive symptoms such as hallucinations and delusions in schizophrenia, its hypofunction resulting from decreased expression or inactivation of dopamine receptors in the prefrontal cortex and caudate nucleus appears to be associated with the development of negative symptoms like anhedonia, lack of motivation, and speech disorders [53,54]. Experimental studies established from the use of antipsychotic drugs that modulate the serotonergic and dopaminergic systems revealed impaired interaction between dopamine and serotonin could prime the abnormal neurochemical events accounting for schizophrenia [55–57]. Furthermore, recent evidence indicates the dysfunctions of GABAergic neurons in the cortex, altered levels of serotonin, and defects in the cholinergic system of the brain during the symptomatic phase of schizophrenia [11,41,58,59]. Recently, increased level of norepinephrine has also been suggested to play a role in the pathophysiology of schizophrenia [60].

Eventually, schizophrenia has a heritable nature as many genetic determinants have been linked to its pathogenesis [61]. The first-degree relatives and offspring of subjects with schizophrenia pose a considerable degree of risk of developing the clinical symptoms [42,61]. However, the genetic linkages and the mutations are not unique among schizophrenia patients. The clinical episodes of schizophrenia have been mapped to various polymorphisms or dysregulation of susceptibility genes such as 1) neuregulin (NGR)-1, a candidate gene involved in brain development, vesicular transport of glutamate and EGF signaling, 2) dystrobrevin-binding protein (DTNBP)-1 which aids in glutamate release, 3) catecholamine O-methyl transferase (COMT), important for signal transduction of dopamine, 4) dopamine beta-hydroxylase (DBH) that catalyzes the hydroxylation of dopamine and some phenylethylamine derivatives and 5) regulator of g-protein signaling (RGS)-9 responsible for various molecular pathways transduction in the brain and 6) the disrupted-in-schizophrenia 1 (DISC1) that is known to interact with factors responsible downstream dopamine signaling pathway and glycogen synthase kinase-3 (GSK-3) [62–67]. Eventually, the suicidal behaviors in schizophrenia have been attributed to defects in genes such as the corticotropin-releasing hormone receptor (CRHR)-1 and corticotropin-releasing hormone binding protein (CRHBP) that encode stress response elements involved in the regulation of the hypothalamic-pituitary-adrenal (HPA)-axis [68]. Notably, the aforementioned neurobiochemical and genetic determinants and risk factors appear to be associated with morphological differences and neuroanatomical abnormalities in schizophrenia.

Neuro morphological and pathological sequelae of schizophrenia

Owing to its obvious abnormalities in neurotransmission, there has been overwhelming data available for the description of the behavioral deformities and psychotic symptoms in schizophrenia [69]. However, the distinct neuropathological changes of schizophrenia arising from various idiopathic factors have long been refractory to the definitive diagnosis. Earlier radiology-based pneumoencephalography attempts revealed dilated lateral and third ventricles in the brains of subjects with schizophrenia [70,71]. Later on, Johnstone et al validated the enlarged brain ventricles using axial brain scans in schizophrenic brains [72]. As considerable scientific and technological advancements made in recent decades, neuroimaging techniques, and neuromorphometric assessments have revealed anatomical, cytoarchitectural alteration, and functional defects in the brains of subjects with and at risk of schizophrenia. In the quest to address the neuropathological changes in the brain of schizophrenia, ample neuroimaging evidence obtained from computed tomography (CT), magnetic resonance imaging (MRI) involved diffusion-tensor imaging (DTI) tractography, and functional imaging, magnetic resonance spectroscopy (MRS), magnetoencephalography (MEG) and positron emission tomography (PET)-based studies convincingly demonstrated and validated enlarged ventricles, grey matter loss, structural deformities and loss in corpus callosum, increased volume in basal ganglia, loss of myelination and dysconnectivity of neural network, differences in neurite curvature among key brain areas in schizophrenia [71,73–75]. Further, a series of MRI-based reports on gross brain morphometric and gyrification assessments unveiled obvious volumetric reduction in the frontal lobe and temporal lobe in schizophrenia subjects [76]. Concomitantly, decreased density of cortical regions and shrinkage in the amygdala, thalamus, nucleus accumbens, and hippocampus have been established as region-

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specific morphological defects in schizophrenia [78,79]. A surface-based MRI analysis by Sprooten et al., 2013 intended the widespread cortical thinning, more predominantly in superior frontal, medial parietal, and lateral occipital regions during the early stages of schizophrenia [80]. A resting-state functional magnetic resonance imaging (rs-fcMRI) based analytical study done by Sheffield et al., 2017 in schizophrenic individuals reported that cognitive impairment is linked to loss of functional connectivity within and between fronto-parietal lob and cingulo-opercular networks [81]. Studies from the magnetic resonance spectroscopy and PET on the brains of schizophrenia patients reported that dopamine and GABA systems primarily contribute to the pathophysiology and development of psychotic disorders, which has been attributed to an excitatory-inhibitory imbalance in the cerebello-thalamo-cortical and striato-thalamo-cortical loops, hyperfunction in the mesolimbic dopamine pathway and differences in dopaminergic content in the prefrontal cortex (PFC), anterior cingulate gyrus, and hippocampus [82,83].

The increased volume of cerebrospinal (CSF) and the possibilities of neurodegeneration have been proposed for the enlarged ventricles in schizophrenia [84]. To note, the enlarged ventricle has been established as a prominent neuropathological mark related to many neurodegenerative processes and tissue remodeling in many neurocognitive diseases as the neuroblasts migrate from the subventricular zone (SVZ) to the degenerating sites [85,86]. At the same time, the corpus callosum helps in connecting and coordinating the functions of two hemispheres, dysconnectivity between functional areas has been assumed to result in schizophrenia [87,88]. While the occurrence of neurodegeneration in schizophrenia has been a long-standing subject of examination, the studies of histopathological correlates of the postmortem brain samples from schizophrenia victims revealed synaptic loss rather than neurodegeneration can be responsible for the volume loss in many brain regions [89]. Eventually, demyelination resulting from the degeneration of oligodendrocytes has been predicted to be the reason for white matter lesions in the frontal cortex, hippocampus, and cerebellum in schizophrenia [56,90]. Among various brain regions, the hippocampus has been considered to play a crucial role in neurocognitive functions as it holds a niche for neural stem cells (NSCs) and regenerative capacity [91,92] . Atrophy or dysfunction of the hippocampus has been linked to dementia, mood, and psychotic disorders [20,33–35,91,92]. Notably, schizophrenia has been characterized by neuroanatomical, cytoarchitectural, synaptic dissociation, demyelination, microglial activation, and functional abnormalities in association with neuroinflammation in the hippocampus [93,94]. Distinctly, the ongoing neurogenesis mediated by NSCs-derived neuroblasts has been reported to play a key role in regenerative plasticity, neurocognitive regulation, memory, and mood functions [92]. Defects in the hippocampal neurogenic process have been linked to dementia, stress, and depression-related symptoms in various neurological illnesses and traumatic brain injuries [20,34,35,39,40,85,93,95]. Eventually, abnormal neurogenesis appears to be associated with neurodevelopmental disorders like autism [96]. Therefore, the possibilities for the involvement of aberrant neurogenesis in the hippocampus in the establishment of psychotic disorders cannot be excluded. Among various, maladaptive disorders, hallucination appears to be a district psychotic symptom predominantly observed in schizophrenia [97]. While the aging-related progressive cognitive decline has been correlated with a steady decline in hippocampal neurogenesis, recent evidence suggests varying degrees of neurogenesis upon the pathogenic progression in mental deterioration and neurodegenerative illnesses that not only display dementia [98]. Notably, schizophrenia has been characterized by arrest in the maturation of the hippocampus due to elevated levels of cellular and molecular signatures of immature neurons [99,100]. Considering the aforementioned facts, the possibilities for the involvement of the regulation of neurogenesis in the hippocampus along with the disease progression could be highly relevant in schizophrenia. Differential regulation, prolonged dysregulation, and impaired neurogenesis may significantly contribute to dysfunctional information processing leading to both cognitive deficits and hallucinations in schizophrenia. Thus, insight into mechanisms associated with hallucinations and impaired neurogenesis might aid in the emergence of future therapeutics to mitigate the disease progression.

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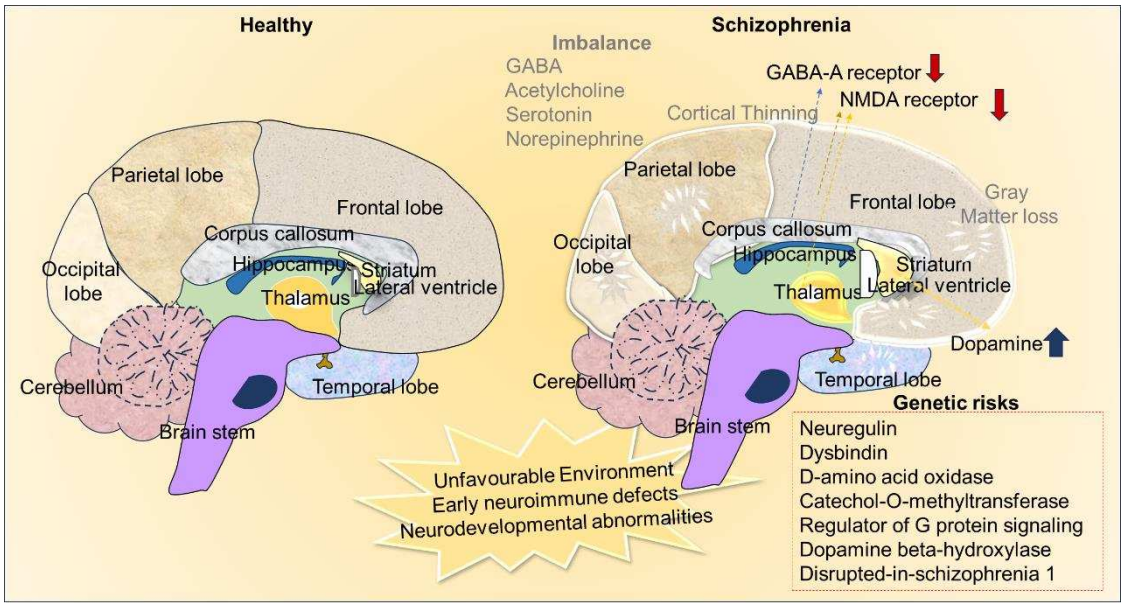

Figure 2. Neurochemical and anatomical differences in healthy and schizophrenia. The image depicts the environmental impact, variations in neurotransmission and hereditary factors as the etiological causes of schizophrenia. Nneuroanatomical alterations such as cortical thinning and loss of grey matter in the schizophrenic brain compare to healthy brains.

Reactive neuroblastosis as an underlying mechanism of hallucination in schizophrenia and other neurological disease

Hallucination is the involuntary generation of illusory, perceptual, and mystical experiences of the brain that occur devoid of external stimuli from the sensory organs and environment [101]. Hallucination can occur at the level of auditory, visual, tactile, olfactory, and gustatory functions during conscious as well as in paradoxical sleeping states. Ample functional neuroimaging studies suggest that the generation of abrupted neural impulses in the key brain areas including the sensory cortex, insula, putamen, and hippocampus could be an underlying cause of hallucination [102–104]. However, the origin of the spontaneous neural activity in the brain that synthesizes substrate for the generation of hallucination remains obscure. Thus far, numerous theories have been postulated for the underlying basis of hallucination [105,106]. For example, Lopez Ibor proposed that abnormal activation of engram, a hypothetical form of substratum essential for the cognitive process in ideational centers of the brain, can be an underlying basis of hallucination [105,107]. According to Hughlings Jackson, the upper motor centers of the brain are involved in intellectual ability when spontaneous activities of the foremost motor centers of the brain independent of peripheral reactions or activation of mid-level motor centers upon deactivation of the upper motor center could result in hallucination [108,109]. As per Wilder Penfield's experimental findings, electrical stimulation in certain cortical or subcortical structures can cause different forms of hallucinations [110,111]. Notably, the occurrence of hallucination is associated with changes in neuroplasticity closely related to key brain regions like primary and secondary sensory cortices, basal ganglia, and limbic system including the hippocampus [112]. Among different neurotransmitter-based hypotheses, varying levels of dopamine in the limbic system have been considered to actively contribute to the development of hallucinations [113]. Recently, abnormal immune activation, increased cerebral blood flow, circulating metabolites, and energy metabolism in the brain have been linked to hallucinations [114–117]. However, most of the theories on hallucinations appear to be merely paradoxical and none of the concepts has been proven to delineate the definite mechanism of hallucination. Therefore, advancement in the understanding of the root cause of hallucination from different perspectives including at the cellular level has become important.

Though hallucination has been ascertained as a foremost psychotic symptom of schizophrenia, it also occurs in many other diseases and arises in response to some substance abuse [113]. Indeed,

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hallucination is a key clinical problem in diverged medical conditions including psychiatric complications and neurodegenerative diseases [118]. Notably, various forms of dementia, bipolar disorder, obsessive-compulsive disorder (OCD), epilepsy, cerebral stroke, brain trauma, migraine, brain lesions, brain tumors, metabolic disorders, and Charles bonnet syndrome have been known to be associated with a considerable degree of incidence with hallucination [119]. Mood disorders like anxiety, stress, depression, and post-traumatic stress disorder (PTSD) have also been linked to hallucinations [120]. In AD, reduced acetylcholinesterase activity in the brain has been predicted as a biochemical cause of hallucinations in a significant percentage of subjects with progressive memory loss [121,122]. Eventually, PD and HD patients have also been reported to experience hallucinations due to an imbalance in dopamine and GABA in the limbic system of the brain [123,124]. However, the occurrence of hallucinations in neuropsychiatric and neurodegenerative disorders is a subject of debate as many drugs that are used for the management therapy of neurological deficits, psychotic problems, sleeping abnormalities, and mood disorders have also been known to induce hallucinations [125]. Eventually, prolonged intake of antiepileptic drugs, antidepressants, anticancer medications, and sleeping pills such as narcotics, steroids, pentoxifylline, tramadol, bromocriptine, sertraline, trazodone, appears to cause hallucinations [126,127]. There is no defined biochemical or molecular pathway ascertained for the incidence of hallucinations. Therefore, understanding a specific pathogenic signature in schizophrenia that overlaps with other neurological diseases and the mode of action of hallucinating drugs could provide a valid clue in understanding the underlying basis of the hallucinations.

During embryogenesis, the generation of neurons from embryonic NSCs-derived neuroblasts plays a key role in neurodevelopmental, whereas pathogenic processes in neurodevelopmental disorders and mental disturbances have been attributed to defects in the early neurogenic process [128,129]. Among various predictions, a potential link between schizophrenia and aberrant neurogenic events responsible for unrecognizable abnormal brain development in early life has been widely considered to have a negative impact in the latter adulthood stage leading to psychiatric disturbance and neurocognitive impairments [31,130,131]. Thus, there has been considerable scientific interest in exploring the alteration of neurogenesis in schizophrenia [132]. In the healthy brain, the degree of neuroblasts generation accounting for the neuroregenerative characteristics has been directly correlated with mental health, intellectual ability, sexual drive, pattern separation, and cognitive functions, including learning and memory [91,133–135]. The immature and differentiating state of neuroblasts has been characterized by the expression of PSA-NCAM, doublecortin, and calretinin in the adult brain [32,136,137]. Though turnover of neurogenesis in the human brain and animal brain has been reported to be dissimilar at the level of neuroblasts generation, occurrence of neurogenesis in adulthood has been demonstrated in human brains [134,138,139].

In general, understanding the regulation of neurogenesis in the human brain has some drawbacks due to the unavailability of healthy brain samples during the critical period and technical disadvantages [140]. However, the persistence and regulation of neuroblasts in the healthy human brain and aberrant levels of neurogenic process in disease conditions have been unequivocally demonstrated [22,138,140,141]. While impaired neurogenesis during fetal development has been linked to intellectual disability disorders, the progressive decline in the neuroblast population followed by the loss of new neurons in the hippocampus has been established as a brain aging and distinct neuropathogenic event along with progressive memory loss [35,91,98,134,135,142,143]. However, the role of aberrant neurogenesis in pathogenic mechanism in neuropsychiatric and neurodegenderative disorders has been less explored. Notably, neurological diseases like epilepsy and cerebral stroke are associated with increased neurogenesis in the hippocampus, unusual migration of neuroblasts in the cortex and striatum, and altered cell fate events in the neurogenic and non-neurogenic areas [36,39]. Notably, a significant percentage of subjects with epileptic seizures and cerebral ischemia have been reported to experience hallucination [144–146]. Besides, physical exercise in a physiological state has been known to enhance cognitive ability via the brain-derived neurotrophic factor (BDNF) mediated neurogenesis [147]. However, aggressive physical exercise appears to exacerbate the disease progression in some neurodegenerative diseases and some

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individuals experience hallucination after vigorous physical activities [148]. Interestingly, elevated levels of BDNF induced by physical exercise, enriched environment, and thorough supplement of neuroprotective agents have been established to facilitate hippocampal neurogenesis as it promotes the proliferation and survival of neuroblasts. Moreover, schizophrenic brains have been characterized by increased level of BDNF which might in part contribute to increased neurogenic events accounting for hallucinations [149].

Interestingly, increased level of neuroblasts proliferation and their ectopic migration has also become increasingly evident in the early phase of neurodegenerative disorders, while the late phase of these disorders with the prominent sign of dementia and depression-related disease have been characterized by diminished level of neuroblasts in the brain [20,33,35,37,96,150]. Notably, the ongoing turnover of neuroblasts has generally been confined to the hippocampus and SVZ-OB system, several reports indicate the possibility for the occurrence and migration of neuroblasts in the other brain regions including the cortex, striatum, and hypothalamus [33,37,151–153]. The presence of astroglial cells in the non-neurogenic areas of the brain has been regarded as an alternate source of NSCs responsible for neurogenic events in different areas of the brain [154]. Recently, the sustaining of non-newly generated terminally undifferentiated neuroblasts with differential neuroplastic nature has also been reported in the brains of some mammals such as dolphins and sheep [155,156]. These quiescent neuroblasts are likely to be activated upon environmental stimuli or during disease progression [20,157]. In disease conditions, the abnormal discharge of proinflammatory cytokine from activated immune cells leads to a cell cycle arrest in NSCs which can cause the stimulation of proliferation in neuroblasts as a compensatory cellular effect [20,35]. Recently, based on the immunohistological findings of the DCX staining in brains of the transgenic animal models of HD, Kandasamy and Aigner proposed a concept known as reactive neruoblastosis which describes an abnormal cellular condition of the brain in which neuroblasts undergo enormous proliferation and ectopic migration in the non-classical neurogenic areas [33,34]. These abnormal cell cycle events have been demonstrated to occur as a result of elevated levels of TGF-β mediated induced quiescent of NSCs as well as neuronal differentiation, owing to its pleiotropic properties [20,35,158]. Besides, Kandasamy and colleagues conceptualized an alternative hypothesis that reactive neuroblastosis might also occur due to the dedifferentiation of neurons in neurodegenerative conditions [150]. Likewise, the level of TGF-β has been reported to be increased during the disease course of schizophrenia [159]. This indicates the possibility of the occurrence of reactive neuroblastosis in schizophrenia. Notably, postmortem studies have revealed reduced cell proliferation by means of a lesser count of Ki 67 and PCNA immunopositive cells in the hippocampus of schizophrenia victims [160]. However, the reduction in the overall cell proliferation did not reflect the number of neuroblasts in the neurogenic area of the brain, as D Barbeau et al., reported that reduction in the number of PSA-NCAM-immunoreactive neuroblasts was confined in the hilar region but not in the DG of brains of schizophrenic subjects [161]. Notably, N M Walton et al in 2012 reported the transition state of immature neurons in the hippocampal DG of CaMKIIα-hKO mice that display behavior abnormalities similar to schizophrenia and bipolar disorder [162,163]. This report also points towards the possibilities for the reactive neuroblastosis in schizophrenia. Interestingly, a recent report from Joen-Rong Sheu et al in 2019 revealed an increased number of DCX-expressing neuroblasts with enhanced dendritic arborization, indicating the surplus amount of interacting neuroblasts in the circuit of the hippocampus in the brains of the maternal immune-activated rodent model of schizophrenia [31]. In corroboration with experimental animal study, they demonstrated an increased level of calretinin-positive cells in the hippocampal DG of postmortem brains of schizophrenia [31]. Eventually, a large number of postmortem data indicated an increased density of interstitial white matter neurons (IWMNs) in the brains with schizophrenia, which could have been derived from the enhanced production of neuroblasts [164]. However, Feng et al indicated the there is no change mRNA expression of neuroblast marker in the schizophrenic brains compared to age matched controls that indicates a compensatory cellular mechanism upon ageing process accounting for interstitial white matter neurons enhanced [165].

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Moreover, the treatment of experimental animals with M108, a potent halogenic compound resulted in increased levels of hippocampal neurogenesis and aggravated the symptoms of schizophrenia [31]. In contrast, suppression of the neurogenic process during the adolescent period delayed the onset and progression of schizophrenia-like symptoms in experimental rats [31]. Also, Ketamine and phencyclidine have been considered as potent hallucinating drugs [166]. Multiple lines of experimental evidence suggest that these hallucination drugs increase hippocampal neurogenesis in the hippocampus. Experimental studies revealed that ketamine treatment increases the number of neuroblasts in the hippocampus [167]. Though repeated phencyclidine treatment has been reported to decrease the survival of neurons, a week later repopulation of the compensatory neurons was evident [168,169]. Besides, ample evidence suggested increased proliferative events in the neuroepithelium of schizophrenia patients, compared to explants from healthy controls [170]. Hong, S. et al. provide experimental evidence that PARP-1 is required for the differentiation of NSCs, while its absence results in defective neurogenesis and behavioral impairments leading to schizophrenia-like phenotype in experimental animal models [171]. Eventually, altered levels of Wnt signaling components that induce cell cycle events are evident in schizophrenia [172]. A recent study conducted using iPSC reported altered Wnt-1 signaling activity, a potent inducer of cell cycle in association with abnormal NPC proliferation and imbalanced differentiation of excitatory and inhibitory neurons leading to neuronal circuit miswiring as the developmental origin of schizophrenia [173]. Moreover, subjects with brain metastatic conditions, a state with the malignant proliferation of neuroblasts and glial cells have been reported to display hallucinations [174]. Therefore. it can be strongly argued that reactive proliferation and dendritic growth of neuroblasts contribute to the pathophysiological of hallucination in schizophrenia. Arnold et al, 2001, conducted a study using olfactory epithelium (OE), a structure that continues to undergo neurogenesis and regulation throughout adult life. In his study, he reported the presence of neurons at different stages of development in the post-mortem OE samples, and an increase in the number of immature neurons was evident in schizophrenic patients [175]. In order to survive, the generation of neuroblasts has to be integrated into existing circuits as failure in the integration of neuroblasts would result in their extinction [176]. Therefore, it can be expected that an increased amount of neuroblast generation would form redundant synapses with existing neurons in a competitive nature. Strikingly, neuroblasts have been considered a potential source of the engram, possess electrical properties, and exhibit synoptical activities even in an immature state [33,34,177]. A surplus number of immature neurons resulting from reactive neuroblostosis may tend to integrate into the existing neuronal circuit or may form an extra neural connection in a provocative manner leading to abnormal synoptical, and metabolic activation in the brain thereby drastically misshaping the synapse and electrical events, and creating dysregulation in the release of neurotransmission in the cognitive centers of the diseased brain. Therefore, ultrastructural findings reported the abnormal formation of synapses in schizophrenia patients could be a result of neuroblastosis events leading to miswiring or abnormal patterns of synaptic connections in the brain. The abnormal neurogenic process at the level of integrating an exceeding number of neuroblasts can be proposed to induce abnormal maladaptive psychotic behaviors specifically hallucination. Whereas failure or defects in the integration of a subset of neuroblasts and their consequent loss could be associated with dementia regardless of neurodegeneration of existing mature neurons in schizophrenia.

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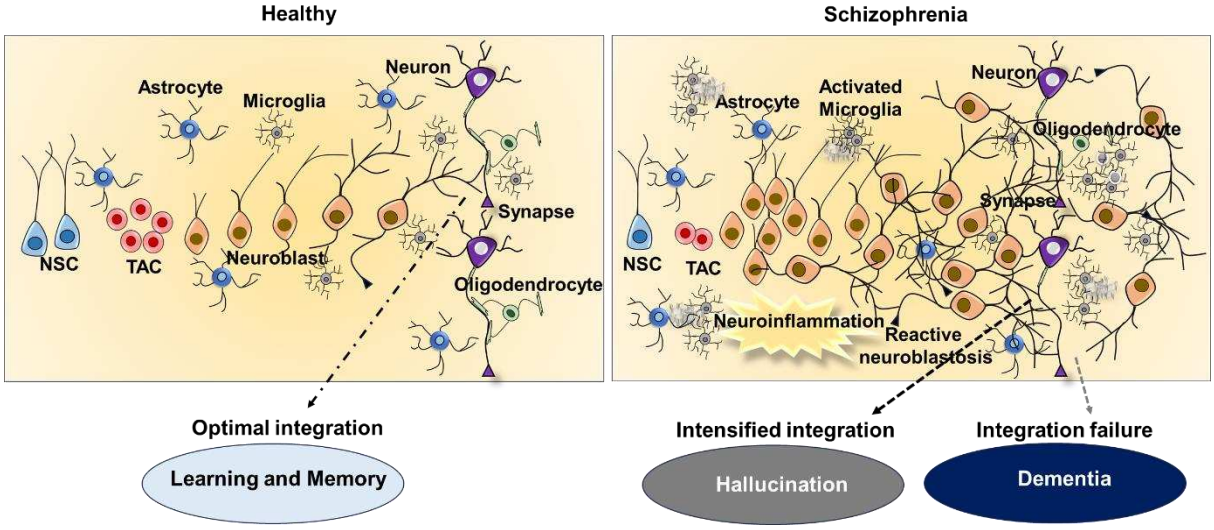

Figure 3. Regulation of adult neurogenesis and reactive neuroblastosis in heathy and schizophrenia brain. The picture provides an overview on the regulation of adult neurogenesis and neuronal integrity in a healthy brain, as well as abnormal neurogenesis and neural integration in schizophrenia. While physiological adult neurogenesis contributes to brain plasticity responsible for cognition function, defective neurogenesis brought on by reactive neuroblastosis causes disruption in neuronal integration and neurotransmission in schizophrenia. Increased neurotransmission from enhanced integration of reactive neuroblasts from could be an underling cause of hallucinations, while decreased neural integration could results in dementia.

Conclusions

The brain is an irreplaceable organ of complex structure that synthesizes dreams, imagination, innovative ideas, and various forms of experiences. Highly structured and regulated forms of neuroplasticity resulting from voluntary and involuntary signals are crucial for motor, physiological, and cognitive performance. Various functional regions of the brain have a great capacity to spontaneously produce neuroplasticity independent of internal and external stimuli. The key functional areas of the brain have the ability to regenerate throughout life. Regulation of NSCs-mediated adult neurogenesis through the generation of neuroblasts has been known to be an integral mechanism for various forms of cognitive functions including intellectual measures, learning, and memory. While various factors can modulate neurogenesis from development to the adult stages, defects in neurogenesis at the level of NSC proliferation and differentiation are associated with various diseases. While known or unknown mutations may alter the cell cycle parameters of the NSC and neuroblasts prolonged activation of immune cells can interfere with their neuronal differentiation and integration process through the proinflammatory and neurotropic factors. Notably, schizophrenia has been linked to an aberrant neurogenic process in the brain. Hallucination is the prime behavioral pathology of schizophrenia and subjects with neurological diseases and intake of some drugs also experience Hallucination for which no confined mechanism has been established. This article emphasizes that reactive neuroblastosis might be responsible for the occurrence of hallucinations as it can abruptly strengthen the synapses and induce abnormal neurotransmission. Besides, failure in the integration of newly generated neuroblasts could contribute to dementia as evidence for neurodegeneration is limited in schizophrenia. Therefore, the futuristic therapeutic targets aimed at harnessing reactive neuroblastosis and correcting the functional integration might be highly beneficial against hallucination and dementia in schizophrenia and other diseases.

Author Contributions: M.K. conceived the idea, and hypothesis and contributed to the framework of the manuscript and illustrations. M.P.B.D.I, J.H.M.J and M.K wrote the initial draft. All contributed to the revision

of the article and made critical comments and suggestions. All authors have read and agreed with this version of the manuscript for submission.

Acknowledgment: MK would like to acknowledge and dedicate this article to the late Palani Murugan Rangasamy, senior scientist, centre for cellular and molecular biology (CCMB), Hyderabad, Telangana, India for inspiration. MK has been supported by the University Grants Commission-Faculty Recharge Programme (UGC-FRP), New Delhi, India. The authors also thank RUSA 2.0, Biological Sciences, Bharathidasan University, for their financial support (TN RUSA: 311/RUSA (2.0)/2018 dt. 2 December 2020).

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